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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,273	02/01/2002	Avi J. Ashkenazi	P3130R1C2	5808

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EXAMINER	
CHERNYSHEV, OLGA N	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,273	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claim 40 has been amended and claim 45 has been cancelled as requested in the amendment filed on September 01, 2004. Claims 40-44 are pending in the instant application.

Claims 40-44 are under examination in the instant office action.

2. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed on July 30, 2004 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

5. Claims 40-44 stand rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for those reasons of record in section 3 of Paper mailed on April 28, 2004. Briefly, the instant application has provided a description of an isolated protein and an antibody to this protein. The instant application does not disclose a specific biological role for these protein and antibody or their significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

Beginning at page 11 of the Response, Applicant summarizes case law on the utility requirement and refers to Utility Examination Guidelines. Applicant's review of the issue of

utility, the case law that has been cited and the holding that is found in that case law is not disputed. The only point of disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

Applicant submits that "the specification provides at least three asserted utilities for PRO444 polypeptides and the claimed antibodies. The first two disclosed utilities are that PRO444 polypeptides induce the expression of c-fos in pericyte cells, and therefore, are useful not only as diagnostic markers for pericyte associated tumors, but also for giving rise to antagonists that are useful for the therapeutic treatment of pericyte associated tumors. Specific antagonists include the claimed antibodies, for example". Further, "the third asserted utility is that PRO444 polypeptides are useful for stimulating angiogenesis. [Accordingly,] the claimed antibodies also have utility in purifying and detecting useful PRO444 polypeptides" (last paragraph at page 13). Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

The first two asserted utilities of the claimed antibodies to PRO444 polypeptides as diagnostic markers for pericyte associated tumors and for the treatment of pericyte associated tumors are based on the results of the assay disclosed in the Example 60, which indicated that PRO444 polypeptide of SEQ ID NO: 9 induced the expression of c-fos in pericyte cells (page 142, Example 60). As fully explained in the previous office action, because the art clearly recognizes that induction of c-fos expression represents a general non-specific first line of cellular response to a variety of stimuli in a variety of cells, one skilled in the art would not attribute the induction of c-fos expression in pericytes by the instant polypeptides as a physiological reaction specifically induced by these particular polypeptides. Accordingly, one

would reasonably conclude that activation of c-fos could not support the assertion of specific, substantial and credible utility of PRO444 antibodies "as diagnostic marker[s] for particular types of pericyte-associated tumors". Furthermore, in view of the lack of evidence that specifically associates the instant PRO444 with any particular type of tumor, including pericyte associated tumors, there appears to be no reasons to conclude that PRO444 antibodies could be used as cancer markers.

Applicant argues that "polypeptides capable of inducing c-fos expression, more specifically the polypeptides that the claimed antibodies bind to, have substantial, specific, and credible use. In particular, the c-fos gene is well known proto-ocogene that is a major target for signal transduction pathways involved in the regulation of cell growth, differentiation, and transformation" (bottom at page 14 of the Response). The Examiner maintains that because activation of c-fos represents a general non-specific cellular response, which is not limited to any particular cell type or particularly associated with a specific physiological function, there appears to be no scientific logic to conclude that the instant PRO444 polypeptides, as inducers of c-fos expression, are involved in tumorgenesis, as asserted in the instant specification. The data presented in the reference cited by Applicant (top at page 15), which indicate that "c-fos deficient cells appear to have intrinsic defect that hinders tumorgenesis", do not support the assertion that any factor capable to induce c-fos expression is involved in tumorgenesis. The instant specification, as filed, fails to present any evidence or sound scientific reasoning to support a conclusion made by Applicant that "the presence of the claimed polypeptides in a subject's tissues or cells (*e.g.,* pericytes) would indicate that the c-fos proto-oncogene is

expressing more c-fos transcription factor that normal, and it is more likely than not that the patient has a malignant tumor" (middle at page 18 of the Response).

Furthermore, the second asserted utility, "the claimed antibodies are useful for neutralizing PRO444's functional activity' (middle at page 15), also appears to be lacking scientific or factual support. Applicant argues that "a skilled artisan would reasonably conclude that a reduction in PRO444 activity would, in turn, minimize the expression of c-fos proto-oncogene, and thus could be used in treatment regiment for a patient suffering from a malignant tumor" (same paragraph, page 15). As fully explained earlier, there appears to be no evidence of record presented in the instant specification, as filed, that would establish the significance of PRO444 c-fos activation in pericytes with relation to a specific physiological activity or a particular pathological condition, including pericyte associated tumors. Thus, regarding the merit of the argument, the instant specification, as filed, provides no evidence to support a conclusion that "[I]n light of their ability to inhibit PRO444 activity, the claimed antibodies possess specific, substantial and credible therapeutic benefits for cancer patients" (bottom at page 15). One skilled in the art readily appreciates that because the instant specification, as filed, has not linked the disclosed PRO444 with any specific disease state or disorder, including cancer in general or pericyte-associated tumors in particular, there appears to be no scientific basis for concluding that an antibody that binds to PRO444 would be useful for treating these diseases. One skilled in the art would be required to perform significant further research on the instant PRO444 polypeptide in order to identify its specific biological activity, significance to a particular disease and, further, to what "use" any information regarding antibodies that bind to PRO444 could be put.

Applicant further submits that "the third asserted use of PRO444 polypeptides [...] relates to their ability to induce angiogenesis, or the formation of new blood vessels. [...] Accordingly, PRO444 polypeptides, purified using the claimed antibodies, can be administered to a patient in need of angiogenesis" (second paragraph on page 16). This is not persuasive because the instant specification discloses that the claimed PRO444 induces c-fos activation and hypothesizes that because c-fos is capable of inducing growth factors that induce the onset of angiogenesis, the PRO444 polypeptides can be used for stimulating angiogenesis. However, there is no disclosure that PRO444 polypeptides are involved in activation of specific pathways that lead to induction of growth factors that further induce the onset of angiogenesis, or that PRO444 are directly involved in stimulating of angiogenesis, as implied in the Response.

Applicant further argues that "Applicants are not required to recite exact tumor types (e.g., breast, brain) that the claimed inventions can treat or diagnose in order to comply with the PTO's utility requirements. There are numerous general treatments (e.g., radiation, chemotherapy) and diagnostics available for cancer that are not limited to exact types of cancer, yet have well established utility" (last paragraph at page 16). This argument has been fully considered but is not deemed persuasive for the following reasons. A specification can meet the legal requirements of utility and enablement for a new polypeptide as long as the specification discloses at least one credible, specific and substantial asserted utility for the new polypeptide, or a well-established utility for the claimed polypeptide would be immediately obvious to the skilled artisan. In the instant case, in view of total lack of evidence or scientific reasoning to support the assertion that the instant PRO444 are specifically associated with cancer in general or with any type of cancer in particular, one skilled in the art would not reasonably believe that

antibodies to PRO444 could be used as a marker for cancer in general or for a specific cancer in particular. Significant further research would have to be conducted to identify diseases or disease states which correlate with activity of the instant PRO444. Therefore, the asserted utility is not applicable to the claimed invention in its currently available form and, consequently, the claimed invention is incomplete and does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

6. Claims 40-44 stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (571) 273-0870. Official papers should NOT be faxed to (571) 273-0870.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.

OLGA N. CHERNYSHEV, PH.D.
PATENT EXAMINER